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A Contemporary Review of Chronic Rhinosinusitis: Pathophysiology, Diagnosis, and Evolving Treatment Strategies

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Abstract: **Introduction:** Chronic rhinosinusitis (CRS) is a multifactorial inflammatory disorder of the nasal and paranasal sinuses that persists for more than 12 weeks, significantly affecting patient quality of life and imposing a substantial healthcare burden. **Methods:** A comprehensive literature review of papers recently published last decade articles was conducted using PubMed, Scopus, and Web of Science. The pathogenesis, diagnosis, treatment, and endotypes of CRS were discussed. This review incorporates peer-reviewed studies and established guidelines while excluding non-English and low-quality publications. **Discussion:** This review provides an accessible yet comprehensive overview tailored for medical students, outlining the current understanding of CRS pathophysiology, including the roles of mucosal barrier dysfunction, microbial dysbiosis, and immune dysregulation. Diagnostic approaches are discussed, with emphasis on clinical evaluation, endoscopic findings, and imaging techniques. Traditional management strategies such as saline irrigation, corticosteroids, and surgical intervention are reviewed alongside emerging biologic therapies and precision medicine approaches. **Conclusion:** Particular attention is given to the evolving classification of CRS into phenotypes and endotypes, which is reshaping treatment algorithms. By integrating current evidence with core clinical principles, this article aims to bridge foundational knowledge with recent advances, enhancing the educational value for early-career clinicians and students.

Key Words: Chronic rhinosinusitis, Functional Endoscopic Sinus Surgery, Endotyping and Phenotyping, Ballon Sinuplasty, Nasla Sinuses

INTRODUCTION

Chronic rhinosinusitis (CRS) is a prevalent and heterogeneous inflammatory condition of the paranasal sinuses and nasal mucosa, affecting approximately 5% to 12% of the global population [1]. Characterized by symptoms persisting for at least 12 weeks—such as nasal obstruction, facial pain or pressure, hyposmia, and mucopurulent nasal discharge, CRS significantly impairs quality of life and imposes substantial healthcare burdens[2].

Traditionally, CRS has been classified into two phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [3]. However, recent advances have led to a more nuanced understanding through the identification of distinct endotypes based on underlying immunopathological mechanisms. These endotypes, characterized by specific inflammatory profiles—such as type 1 (Th1), type 2 (Th2), and type 3 (Th17) responses—highlight the complexity and variability of CRS across different populations and geographic regions[4].

The pathogenesis of CRS is multifactorial, involving a complex interplay between host factors and environmental influences. Key hypotheses include epithelial barrier dysfunction, immune dysregulation, microbial colonization, and the formation of biofilms. Notably, epithelial cells are not merely passive barriers but actively participate in immune responses, with their dysfunction contributing to chronic inflammation[1,5].

Diagnostic evaluation of CRS encompasses a combination of clinical assessment, nasal endoscopy, and imaging studies, particularly computed tomography (CT) scans, to assess the extent of sinus involvement[4] . Management strategies have evolved from conventional medical therapies—such as intranasal corticosteroids and saline irrigation—to include endoscopic sinus surgery for refractory cases. Furthermore, the advent of biologic agents targeting specific inflammatory pathways offers promising therapeutic avenues for patients with severe, treatment-resistant CRS [6].

This review aims to provide medical students and junior clinicians with a comprehensive overview of CRS, integrating current insights into its pathophysiology, diagnostic approaches, and emerging treatment modalities. By elucidating the complex mechanisms underlying CRS and highlighting recent advancements in management, this article seeks to enhance understanding and inform clinical practice in otolaryngology.

Objectives

This review aims to:

- Understand the pathophysiology and classification of chronic rhinosinusitis (CRS), based on the newly published data
- Recognize current updated diagnostic and treatment strategies for CRS
- Integrate foundational knowledge with recent advances to enhance clinical understanding and decision-making in the management of CRS

MATERIALS AND METHODS

A comprehensive literature review was conducted to identify relevant studies on chronic rhinosinusitis (CRS) using databases including PubMed, Scopus, and Web of Science. A variety of keyword combinations, such as "chronic rhinosinusitis," "pathophysiology," "diagnosis," "treatment," "biologic therapy," and "endotypes," were utilized. This study incorporates peer-reviewed English-language research published in the last 10 years, emphasizing recent developments, clinical guidelines, and comprehensive reviews. To ensure a thorough and up-to-date overview, supplementary sources were identified through a manual review of the references in key publications. The inclusion criteria included peer-reviewed original studies, systematic reviews, meta-analyses, and clinical guidelines that address CRS pathophysiology, diagnosis, classification, and management. Exclusion criteria comprised non-English publications, case reports, letters to the editor, conference abstracts, and studies that lacked clinical relevance or scientific rigor.

Pathogenesis of Chronic Rhinosinusitis

Overview of CRS Pathogenesis: Chronic rhinosinusitis (CRS) is a multifactorial inflammatory disorder of the sinonasal mucosa, persisting for at least 12 weeks. It is traditionally categorized into two phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [3]. However, recent insights have revealed a spectrum of endotypes based on underlying immunopathological mechanisms, including type 1 (Th1), type 2 (Th2), and type 3 (Th17) inflammatory responses. This endotypic classification underscores the heterogeneity of CRS and its varied clinical presentations across different populations [3]. The main parameters of old and recent classification are shown in Table 1.

Epithelial Barrier Dysfunction

The sinonasal epithelium serves as a critical barrier against environmental insults. In CRS, this barrier is often compromised, leading to increased permeability and exposure to pathogens. Studies have demonstrated reduced expression of tight junction proteins, such as occludin and zonula occludens-1, in CRS patients, particularly those with nasal polyps. This disruption facilitates the translocation of allergens and microbes, perpetuating chronic inflammation [7].

Role of Innate Immunity

Beyond serving as a physical barrier, the sinonasal epithelium actively participates in innate immune responses. It expresses pattern recognition receptors, including Toll-like receptors (TLRs), which detect pathogen-associated molecular patterns. Activation of these receptors leads to the production of antimicrobial peptides and pro-inflammatory cytokines, orchestrating the initial immune response [8].

Type 2 Inflammation and Eosinophilic Dominance

Type 2 (Th2) inflammation is a hallmark of CRSwNP, characterized by elevated levels of interleukins IL-4, IL-5, and IL-13. These cytokines promote eosinophil recruitment and activation, contributing to tissue edema and polyp formation. Eosinophils release cytotoxic granules and extracellular traps, exacerbating mucosal damage and sustaining inflammation [9].

Non-Type 2 Inflammation: Neutrophilic Involvement

In contrast, CRSsNP often exhibits a non-type 2 inflammatory profile, with a predominance of neutrophils and Th1/Th17 cytokines, such as interferon-gamma (IFN-γ) and interleukin-17 (IL-17). Neutrophils contribute to mucosal damage through the release of proteases and reactive oxygen species, perpetuating the inflammatory milieu [10].

Microbial Factors and Biofilms

Microbial colonization, particularly by Staphylococcus aureus, has been implicated in CRS pathogenesis. These bacteria can form biofilms—structured communities encased in a protective matrix—that resist host defenses and antibiotic treatment. Biofilms serve as reservoirs for persistent infection and chronic inflammation [11].

Superantigens and Immune Activation
Staphylococcus aureus also produces superantigens, which can non-specifically activate T cells, leading to massive cytokine release and amplification of the inflammatory response. This mechanism is particularly relevant in CRSwNP, where superantigen exposure correlates with disease severity and recurrence [12].

Epithelial-to-Mesenchymal Transition (EMT)
EMT is a process wherein epithelial cells acquire mesenchymal characteristics, enhancing their migratory capacity and resistance to apoptosis. In CRS, EMT contributes to tissue remodeling and fibrosis, particularly in the context of chronic inflammation and epithelial injury [13].

Role of Mast Cells and Basophils
Mast cells and basophils are key effector cells in allergic inflammation. Upon activation, they release histamine, proteases, and cytokines, including IL-4 and IL-13, further propagating type 2 inflammation. Their presence is notably increased in CRSwNP, correlating with disease severity [14].

Fibrosis and Tissue Remodeling
Chronic inflammation in CRS leads to tissue remodeling, characterized by fibrosis, glandular hyperplasia, and extracellular matrix deposition. These changes contribute to the persistence of symptoms and resistance to conventional therapies. Understanding the mechanisms underlying tissue remodeling is crucial for developing targeted interventions [15].

Diagnosis of Chronic Rhinosinusitis: Emerging Trends and Innovations
Traditional Diagnostic Criteria and Limitations: Chronic rhinosinusitis (CRS) is traditionally diagnosed based on clinical symptoms persisting for at least 12 weeks, including nasal obstruction, nasal discharge, facial pain or pressure, and reduction or loss of smell. These symptoms are corroborated by objective findings from nasal endoscopy or computed tomography (CT) scans. However, symptom-based diagnosis can be subjective and may not accurately reflect the underlying pathophysiology, leading to potential misdiagnoses or suboptimal treatment strategies [16]. To overcome the limitations and of the traditional techniques, new trends were developed for better diagnosis of the patients of CRS. The major differences among the traditional and recent approaches are summarized in Table 2.

Nasal Endoscopy and Imaging Modalities
Nasal endoscopy allows direct visualization of the nasal cavity and sinus ostia, aiding in the detection of mucosal edema, purulent discharge, and nasal polyps. CT imaging, particularly of the paranasal sinuses, provides detailed anatomical information and is instrumental in surgical planning. The Lund-Mackay scoring system is commonly used to quantify the extent of sinus disease on CT scans [17].

Endotyping and Biomarker Identification
Recent research emphasizes the importance of identifying distinct endotypes of CRS, characterized by specific immunopathological mechanisms. Biomarkers such as eosinophil counts, cytokine profiles (e.g., IL-5, IL-13), and immunoglobulin E (IgE) levels have been investigated to differentiate between type 2 and non-type 2 inflammation. This stratification facilitates personalized treatment approaches, including the use of targeted biologic therapies [18].

Proteomics and Metabolomics Applications
Advancements in mass spectrometry have enabled proteomic and metabolomic analyses of nasal secretions and tissues, uncovering potential diagnostic and prognostic biomarkers for CRS. These molecular-level insights contribute to a better understanding of disease mechanisms and may lead to the development of non-invasive diagnostic tools [3].

Artificial Intelligence and Machine Learning Integration
Artificial intelligence (AI) and machine learning algorithms are increasingly applied to CRS diagnosis, particularly in interpreting imaging data. Deep learning models have demonstrated proficiency in predicting CRS endotypes and assessing disease severity from CT scans, potentially enhancing diagnostic accuracy and aiding in treatment planning [19].

Genomic and Taste Receptor Studies
Genetic studies have identified associations between CRS and specific gene polymorphisms, including those related to taste receptors like TAS2R38. These receptors, expressed in the sinonasal epithelium, may influence innate immune responses to bacterial pathogens. Understanding such genetic factors could lead to novel diagnostic markers and therapeutic targets [20].

Nasal Nitric Oxide Measurement
Nasal nitric oxide (nNO) levels have been explored as a non-invasive biomarker for CRS. Reduced nNO levels are often observed in patients with nasal polyps and may reflect impaired sinus ventilation or mucosal inflammation. While promising, standardization of measurement techniques and interpretation is necessary for clinical application [21].

Microbiome Analysis
The sinonasal microbiome plays a crucial role in maintaining mucosal health. Dysbiosis, or microbial imbalance, has been implicated in CRS pathogenesis. Advanced sequencing technologies allow for detailed microbiome profiling, which may aid in diagnosis and inform probiotic or antimicrobial therapies [22].

Table 1: The Main Parameters of Old and Recent Classifications of Chronic Rhinosinusitis [1-3]

Aspect	Traditional Classification	Recent (Updated) Classification
Basis of Classification	Clinical phenotype based on nasal polyp presence	Immunological and molecular endotypes + clinical phenotypes
Main Categories	CRS with Nasal Polyps (CRSwNP) - CRS without Nasal Polyps (CRSsNP)	Type 2 (eosinophilic, Th2-mediated) - Non-Type 2 (neutrophilic or non-Th2)
Diagnostic Focus	Endoscopic and radiologic findings	Biomarkers (e.g., eosinophils, IgE, IL-5), cytokine profiles
Treatment Implications	Similar treatments within phenotypes	Personalized treatment (e.g., biologics for Type 2 inflammation)
Limitations	Overly simplistic, poor prediction of treatment response	Greater precision but requires advanced testing and resources
Clinical Utility	Basic clinical guidance	Supports precision medicine and targeted biologic therapy

Table 2: Comparison Among the Traditional and Recent Diagnostic Approaches for Chronic Rhinosinusitis [16-23]

Diagnostic Aspect	Traditional Methods	Recent Advances
Clinical Evaluation	Symptom-based (≥12 weeks of nasal congestion, discharge, etc.)	Symptom scoring systems (e.g., SNOT-22, EPOS criteria integration)
Nasal Examination	Anterior rhinoscopy or basic endoscopy	High-resolution nasal endoscopy with digital documentation
Imaging	Plain sinus X-rays (historically) CT scan (standard)	Cone beam CT Image-guided navigation for pre-surgical planning
Microbiological Testing	Culture from nasal swab or lavage (limited use)	Molecular diagnostics (e.g., PCR-based detection of pathogens)
Allergy/Immunologic Workup	Basic skin prick tests or serum IgE levels	Component-resolved diagnostics (CRD) for detailed allergen profiles
Inflammatory Markers	Not routinely assessed	Biomarker analysis (e.g., blood or tissue eosinophils, IL-5, IgE)
Classification Tools	Based on presence/absence of polyps	Endotyping via cytokine profiling, tissue histopathology
Diagnostic Limitations	Symptom overlap with other disorders	Need for resource-intensive techniques and biomarker standardization

Role of Patient-Reported Outcome Measures

Incorporating patient-reported outcome measures (PROMs), such as the Sino-Nasal Outcome Test (SNOT-22), provides valuable insights into symptom burden and treatment efficacy from the patient's perspective. These tools complement objective findings and support a holistic approach to CRS management [23].

Future Directions in CRS Diagnosis

The integration of multi-omics data, AI-driven analytics, and personalized medicine principles heralds a new era in CRS diagnosis. Ongoing research aims to refine endotype classifications, validate novel biomarkers, and develop predictive models to optimize patient outcomes. Collaborative efforts across disciplines will be essential in translating these advancements into clinical practice [24].

New Trends in the Treatment of Chronic Rhinosinusitis: Innovations in Functional Endoscopic Sinus Surgery and Emerging Therapies

Chronic rhinosinusitis (CRS) is a prevalent inflammatory condition of the paranasal sinuses, significantly impacting patients' quality of life. Traditional management strategies have included medical therapies such as antibiotics and corticosteroids, with Functional Endoscopic Sinus Surgery (FESS) reserved for refractory cases. Recent advancements have introduced novel surgical techniques, biologic therapies, and innovative drug delivery systems, reshaping the therapeutic landscape of CRS [25].

Advancements in Functional Endoscopic Sinus Surgery (FESS)

Functional Endoscopic Sinus Surgery (FESS) continues to be a pivotal intervention for patients with chronic rhinosinusitis (CRS), particularly those unresponsive to medical therapy. Recent studies have underscored its efficacy in improving patient-reported outcomes and quality of life [26]. For instance, a study analyzing concurrent septorhinoplasty and FESS procedures found that both surgeries, individually and combined, significantly enhanced disease-specific quality of life without compromising outcomes[27] . Moreover, research has highlighted the importance of preoperative assessments; elevated immunoglobulin E (IgE) and eosinophil levels have been associated with a prolonged need for postoperative intranasal steroid treatments, suggesting that immunological profiling can inform postoperative management strategies [28].

Advancements in perioperative care have also contributed to optimizing FESS outcomes. A systematic review revealed that perioperative lidocaine infusion significantly improved the surgical field's quality and expedited post-anesthesia care unit (PACU) discharge times, although it did not affect surgery duration or estimated blood loss [29]. Additionally, the choice of anesthesia technique plays a crucial role; total intravenous anesthesia (TIVA) has been associated with better hemostasis and surgical field visibility compared to inhalational anesthesia, thereby facilitating more efficient surgical procedures [30].

Identifying patients at risk for revision surgery remains a critical focus. A multivariate analysis identified factors such as asthma, aspirin sensitivity, smoking, and eosinophilia as significant predictors for the need for revision FESS [26]. Furthermore, histopathological evaluations have provided insights into treatment resistance; patients with persistent symptoms despite biologic therapy exhibited distinct tissue characteristics, indicating the necessity for tailored surgical approaches in this subset . These findings emphasize the importance of personalized treatment plans based on individual risk profiles and disease phenotypes [30].

Balloon Sinuplasty: A Minimally Invasive Alternative

Balloon Sinuplasty (BSP) has emerged as a minimally invasive alternative to traditional Functional Endoscopic Sinus Surgery (FESS) for the treatment of chronic rhinosinusitis (CRS), particularly in patients with limited disease and without extensive nasal polyposis. This technique involves the use of a balloon catheter to dilate the sinus ostia, thereby restoring normal sinus drainage while preserving mucosal integrity [31]. Clinical studies have demonstrated the efficacy of BSP in improving patient outcomes. A prospective clinical study involving 20 patients reported significant symptom improvement, as measured by the Sino-Nasal Outcome Test (SNOT-20), and objective findings on diagnostic nasal endoscopy and CT scans over a 12-month follow-up period[32] . Similarly, a retrospective study with a four-year follow-up of 110 patients indicated sustained symptom relief and improved endoscopic and radiological scores, highlighting the long-term benefits of BSP [32] .

Comparative analyses between BSP and FESS have shown that BSP offers comparable symptom relief with the added advantages of reduced postoperative pain, shorter recovery times, and fewer complications. A randomized controlled trial found that BSP was non-inferior to FESS in terms of symptom improvement and superior regarding postoperative debridement rates[33] . The safety profile of BSP is notable, with low complication rates reported across multiple studies. Its minimally invasive nature allows for procedures to be performed in office settings under local anesthesia, making it a viable option for patients who are poor candidates for general anesthesia[34] .

However, the applicability of BSP in pediatric populations remains under investigation. While some studies suggest potential benefits, others highlight the need for further research to establish its efficacy and cost-effectiveness in children [32] . In conclusion, Balloon Sinuplasty represents a significant advancement in the surgical management of chronic rhinosinusitis, offering effective symptom relief with a favorable safety profile. Ongoing research and long-term studies will further delineate its role across diverse patient populations.

Drug-Eluting Sinus Implants

Drug-eluting sinus implants have emerged as a significant advancement in the management of chronic rhinosinusitis (CRS), particularly in enhancing postoperative outcomes and reducing the need for systemic medications. These implants, primarily bioabsorbable and corticosteroid-eluting, are designed to deliver localized, sustained-release anti-inflammatory therapy directly to the sinus mucosa, thereby minimizing systemic side effects and promoting mucosal healing [35].Clinical studies have demonstrated the efficacy of these implants in improving postoperative outcomes. For instance, a randomized controlled trial evaluating the mometasone furoate-eluting sinus implant showed significant reductions in nasal obstruction and polyp grade compared to controls, along with a decreased need for revision surgery [36]. Similarly, in-office placement of steroid-eluting bioabsorbable implants post-endoscopic sinus surgery (ESS) has been shown to be safe, well-tolerated, and effective in reducing ethmoid sinus inflammation and improving patient-reported outcomes [37] .

Comparative studies have also highlighted the benefits of steroid-eluting stents over traditional postoperative packing materials. A study comparing bioabsorbable steroid-eluting sinus stents with absorbable Nasopore packs found that the stents significantly reduced the need for postoperative surgical intervention, polyp formation, and severe adhesions [35]. The use of these implants has also been associated with economic benefits. A budget impact analysis indicated that incorporating bioabsorbable drug-eluting sinus implants post-ESS had a negligible impact on the budget of a self-insured employer or payer, with upfront costs offset by savings from reduced polyp recurrence and adhesion formation [37]. In summary, drug-eluting sinus implants represent a valuable addition to the therapeutic arsenal for CRS, offering targeted therapy that enhances surgical outcomes and patient quality of life. Ongoing research and long-term studies will further elucidate their role in various CRS subtypes and patient populations.

Exhalation Delivery Systems (EDS)

Exhalation Delivery Systems (EDS), particularly those delivering fluticasone propionate (EDS-FLU), represent a significant advancement in the treatment of chronic rhinosinusitis (CRS), especially for patients with nasal polyps (CRSwNP)[38]. By utilizing the patient's exhaled breath to propel medication into the nasal cavities, EDS devices achieve deeper and more targeted drug delivery compared to conventional nasal sprays. This method enhances the deposition of corticosteroids in the posterior and superior regions of the nasal passages, areas often challenging to reach with standard delivery systems [39]. Clinical trials have demonstrated the efficacy of EDS-FLU in improving both objective and subjective outcomes in CRS patients. A randomized, double-blind study reported significant improvements in nasal congestion, polyp grade, and quality of life measures, with a notable reduction in the number of patients eligible for surgery. Furthermore, a 12-month open-label study observed sustained symptom improvement, with 87% of patients reporting benefits and over half experiencing polyp elimination in at least one nostril [40].

EDS-FLU has also shown promise in patients with prior endoscopic sinus surgery (ESS). Pooled analyses from two large controlled trials indicated that both surgery-naïve and post-ESS patients experienced significant symptom relief and quality-of-life improvements with EDS-FLU treatment. This suggests that EDS-FLU can be an effective therapeutic option regardless of surgical history [41]. Safety profiles of EDS-FLU are comparable to traditional intranasal corticosteroids. A comprehensive evaluation of ocular safety found minimal risk of elevated intraocular pressure or cataract formation, aligning with the safety expectations of corticosteroid therapies. Additionally, common adverse events such as epistaxis and nasal irritation were infrequent and generally

mild [39] In summary, Exhalation Delivery Systems with fluticasone offer a targeted, effective, and safe treatment modality for chronic rhinosinusitis, particularly in patients with nasal polyps. Their ability to deliver medication to hard-to-reach areas of the nasal cavity addresses a significant limitation of conventional therapies, potentially reducing the need for surgical interventions and improving patient outcomes.

Biologic Therapies: Targeting Type 2 Inflammation

Targeting type 2 (T2) inflammation has revolutionized the management of chronic rhinosinusitis with nasal polyps (CRSwNP), particularly in patients unresponsive to conventional therapies. T2 inflammation is characterized by elevated levels of cytokines such as interleukin (IL)-4, IL-5, and IL-13, leading to eosinophilic infiltration and persistent mucosal inflammation. This endotype is predominant in Western populations, accounting for over 80% of CRSwNP cases [42] Biologic therapies targeting T2 cytokines have emerged as effective treatments for severe CRSwNP. Dupilumab, an IL-4 receptor alpha antagonist, inhibits IL-4 and IL-13 signaling pathways, resulting in significant reductions in polyp size and improvements in nasal congestion and olfactory function . Similarly, anti-IL-5 agents like mepolizumab and reslizumab, and anti-IL-5 receptor agents such as benralizumab, have demonstrated efficacy in reducing eosinophilic inflammation and polyp burden [43].

The selection of appropriate candidates for biologic therapy is crucial. Biomarkers such as blood eosinophil counts, serum IgE levels, and nasal cytokine profiles can aid in identifying patients with T2 inflammation who are likely to benefit from these treatments . However, approximately 40–60% of patients may not respond adequately, highlighting the need for precise endotyping and personalized treatment approaches [44]. Recent research has explored the role of epithelial-derived alarmins, including thymic stromal lymphopoietin (TSLP) and IL-33, in initiating T2 inflammatory responses. Biologics targeting these upstream mediators, such as tezepelumab (anti-TSLP), are under investigation and may offer broader anti-inflammatory effects by modulating the activation of innate lymphoid cells and Th2 cells [45].

The integration of biologics into treatment algorithms necessitates a multidisciplinary approach, considering factors such as disease severity, comorbidities (e.g., asthma), prior surgical interventions, and patient preferences. In cases of refractory CRSwNP, biologics may serve as an alternative or adjunct to revision surgery, potentially reducing the need for invasive procedures [46]. Long-term studies have affirmed the sustained efficacy and safety of biologic therapies. For instance, extended use of dupilumab has been associated with continued symptom improvement and a low incidence of adverse events over a 48-month period . These findings support the role of biologics as a viable long-term treatment option for patients with severe CRSwNP [47].

Despite these advancements, challenges remain in managing patients with mixed or non-T2 inflammatory endotypes. Approximately 50% of Asian CRSwNP patients exhibit non-T2 inflammation, necessitating the development of novel therapies targeting alternative pathways, such as type 1 and type 3 cytokines . Understanding the heterogeneity of CRS endotypes is essential for optimizing treatment outcomes [48,49]. In conclusion, targeting T2 inflammation with biologic therapies has significantly improved the management of severe CRSwNP. Ongoing research into biomarkers, novel therapeutic targets, and personalized treatment strategies will further enhance the ability to tailor interventions to individual patient profiles, ultimately improving quality of life for those affected by this chronic condition.

Personalized Medicine and Endotyping

Understanding the heterogeneity of CRS has led to the identification of distinct endotypes based on underlying inflammatory pathways. This stratification enables personalized treatment approaches, optimizing therapeutic efficacy and minimizing unnecessary interventions[50, 51] .

Integration of Multimodal Therapies

Combining surgical interventions with adjunctive therapies, such as biologics and targeted drug delivery systems, offers a comprehensive approach to CRS management. This multimodal strategy addresses both the anatomical and inflammatory components of the disease, enhancing overall treatment outcomes [52, 53].

Strengths of the Review

This review integrates clinical findings and recent advancements in molecular biology, immunopathology, and diagnostic technologies to present a comprehensive and up-to-date overview of chronic rhinosinusitis (CRS). The integration of clinical perspectives with concepts such as immunological endotyping, epithelial-mesenchymal transition (EMT), and microbiome-host interactions constitutes a significant strength. The manuscript situates complex findings such as biologics and omics-driven diagnostics within a practical clinical context, ensuring its relevance for both academic and clinical audiences. The inclusion of artificial intelligence and precision medicine perspectives highlights the review's prospective, translational significance and the evolving landscape of CRS management. A critical examination of the limitations of existing classification and management options establishes a robust foundation for CRS research and therapeutic innovation.

Constraints of the Review

The review offers a comprehensive and current overview of CRS; however, its narrative format may lead to selection bias and does not possess the methodological rigor characteristic of a systematic review. The integration of emerging technologies, including artificial intelligence and omics-based diagnostics, remains largely conceptual, with minimal discourse on their present clinical applicability and accessibility in routine practice.

CONCLUSION

CRS pathogenesis is now understood to be multifactorial, involving disrupted epithelial barrier function, dysregulated host-microbial interactions, and a spectrum of immune responses. In particular, the role of type 2 (T2) inflammation, characterized by eosinophilic infiltration and IL-4, IL-5, and IL-13 cytokine activity, is dominant in many patients, especially those with nasal polyps and comorbid asthma or AERD.

Advancements in diagnostic techniques—including high-resolution imaging, nasal endoscopy, and biomarker profiling—have enhanced our ability to accurately classify CRS into clinically meaningful phenotypes and endotypes. Novel diagnostic tools, including exhalation delivery systems (EDS), point-of-care biomarker assays, and emerging omics-based approaches, hold promise for earlier and more precise detection.

Therapeutically, the landscape has shifted significantly. While functional endoscopic sinus surgery (FESS) remains central in managing patients unresponsive to medical therapy, a growing arsenal of innovative treatments—such as balloon sinuplasty, drug-eluting implants, exhalation-based steroid delivery, and targeted biologics—has provided less invasive and more tailored options. Targeting T2 inflammation with biologics has proven especially beneficial in reducing polyp burden and improving symptoms in refractory cases.

Recommendations and Future Directives

To optimize the management of chronic rhinosinusitis (CRS), clinical practice should evolve to incorporate an endotype-based approach, enabling differentiation between T2-high and non-T2 disease through immunologic profiling, thereby informing both medical and surgical strategies. Multidisciplinary collaboration among otolaryngologists, allergists, and pulmonologists is essential, particularly in cases with overlapping respiratory or allergic comorbidities, to ensure comprehensive and coordinated care. Diagnostic accuracy can be enhanced through standardized algorithms that combine symptom scoring tools (e.g., SNOT-22), radiologic assessments (e.g., Lund-Mackay score), and emerging biomarkers within structured evaluation protocols. Surgical intervention, particularly functional endoscopic sinus surgery (FESS), should be refined by integrating disease severity, anatomical factors, and endotypic classification, and increasingly complemented by adjunctive therapies such as biologics or drug-eluting implants to improve long-term outcomes. The incorporation of novel drug delivery systems, including balloon sinuplasty and exhalation delivery systems (EDS), offers minimally invasive alternatives or adjuncts to conventional pharmacotherapy, particularly in carefully selected patient populations. Finally, biologic therapies should be personalized using validated biomarkers, disease burden, and prior treatment history, with clearly defined protocols for post-treatment monitoring and criteria for continuation to ensure sustained therapeutic benefit.

Future directions in chronic rhinosinusitis (CRS) management should focus on developing targeted therapies for non-T2 inflammation, including neutrophilic or type 1/3 dominant pathways, to address the disease's heterogeneity, especially in Asian populations and other specific subgroups. Developing affordable and accessible biomarkers is essential for enhancing diagnosis, predicting therapy responses, and monitoring disease progression, thereby advancing biomarker-driven precision medicine. The integration of digital tools and artificial intelligence into diagnostic processes, such as endoscopic image analysis, radiologic assessment, and electronic health record data mining, holds potential for improving diagnostic accuracy and clinical efficiency. Utilizing CRS registries and prospective cohort studies will generate longitudinal, real-world data sources that provide valuable analysis of long-term effects and treatment efficacy. Examining mixed modality trials that assess the synergistic effects of biologics in conjunction with localized drug delivery devices or surgical interventions may further reduce recurrence rates. Ultimately, optimizing outcomes and minimizing the overall burden of illness will rely on the implementation of patient-centered care models that facilitate shared decision-making, monitor treatment adherence, and tailor interventions to meet individual needs.

Chronic rhinosinusitis is no longer managed through a "one-size-fits-all" approach. The intersection of immunologic insights, technological innovation, and precision diagnostics has transformed the field. Continued research, education, and integration of emerging therapies into practice will be essential to improve the lives of patients suffering from this complex and chronic disease.

REFERENCES

[1] Fokkens, W.J. *et al.* "European position paper on rhinosinusitis and nasal polyps 2020." *Rhinology journal,* vol. 0, February 2020, pp. 1-464. http://dx.doi.org/10.4193/rhin20.600.

[2] Black, Kevin J. *F1000research: Tics welcomes you to 21st century biomedical publishing.* 2014. http://dx.doi.org/10.12688/f1000research.5664.1.

[3] Guo, Shudi *et al.* "Recent advances in mass spectrometry-based proteomics and metabolomics in chronic rhinosinusitis with nasal polyps." *Frontiers in Immunology,* vol. 14, September 2023. http://dx.doi.org/10.3389/fimmu.2023.1267194.

[4] Du, W. *et al.* "Deep learning in computed tomography to predict endotype in chronic rhinosinusitis with nasal polyps." *BMC Med Imaging.* Vol. 24, no. 1, 2024, pp. 25. https://doi.org/10.1186/s12880-024-01017-7

[5] Avdeeva, Klementina, and Wytske Fokkens. "Precision medicine in chronic rhinosinusitis with nasal polyps." *Current Allergy and Asthma Reports,* vol. 18, no. 4, March 2018. http://dx.doi.org/10.1007/s11882-018-0776-8.

[6] Marple, Bradley F. *et al.* "Diagnosis and management of chronic rhinosinusitis in adults." *Postgraduate Medicine,* vol. 121, no. 6, November 2009, pp. 121-139. http://dx.doi.org/10.3810/pgm.2009.11.2081.

[7] Dam, Jonas B. van, and Anna M. Ehlers. "Memory b cells with extraordinary longevity upon smallpox vaccination: Implications for type 1 hypersensitivities." *Allergy,* vol. 78, no. 10, June 2023, pp. 2805-2807. http://dx.doi.org/10.1111/all.15777.

[8] Czerwaty, Katarzyna *et al.* "Immunological aspects of chronic rhinosinusitis." *Diagnostics,* vol. 12, no. 10, September 2022, pp. 2361-0. http://dx.doi.org/10.3390/diagnostics12102361.

[9] Li, William *et al.* "Evaluation of diffuse type 2 dominant or eosinophilic chronic rhinosinusitis with corticosteroid irrigation after surgical neosinus cavity formation." April 2021. http://dx.doi.org/10.1001/jamaoto.2020.5286.

[10] Lyons, Jonathan J. *et al.* "Heritable risk for severe anaphylaxis associated with increased α-tryptase–encoding germline copy number at tpsab1." *Journal of Allergy and Clinical Immunology,* vol. 147, no. 2, February 2021, pp. 622-632. http://dx.doi.org/10.1016/j.jaci.2020.06.035.

[11] Michalik, Michał, and Beata Krawczyk. "Chronic rhinosinusitis—microbiological etiology, potential genetic markers, and diagnosis." *International Journal of Molecular Sciences,* vol. 25, no. 6, March 2024, pp. 3201-0. http://dx.doi.org/10.3390/ijms25063201.

[12] Kato, Atsushi, and Hirohito Kita. "The immunology of asthma and chronic rhinosinusitis." *Nature Reviews Immunology,* vol. 25, no. 8, April 2025, pp. 569-587. http://dx.doi.org/10.1038/s41577-025-01159-0.

[13] "Tgf-β1 induces epithelial-to-mesenchymal transition in chronic rhinosinusitis with nasal polyps through microrna-182." *Asian Pacific Journal of Allergy and Immunology,* vol. 42, no. 1, 2024, pp. 61-73. http://dx.doi.org/10.12932/ap-040921-1224.

[14] Kita, Hirohito. "How are airborne allergens remembered by the immune system?." *Journal of Allergy and Clinical Immunology,* vol. 149, no. 6, June 2022, pp. 1940-1942. http://dx.doi.org/10.1016/j.jaci.2022.02.014.

[15] Amirapu, Satya *et al.* "Sinonasal tissue remodelling during chronic rhinosinusitis." *International Journal of Otolaryngology,* vol. 2021, September 2021, pp. 1-9. http://dx.doi.org/10.1155/2021/7428955.

[16] Szaleniec, Joanna *et al.* "Challenging the gold standard: Methods of sampling for microbial culture in patients with chronic rhinosinusitis." *European Archives of Oto-Rhino-Laryngology,* vol. 278, no. 12, March 2021, pp. 4795-4803. http://dx.doi.org/10.1007/s00405-021-06747-z.

[17] Hildenbrand, Tanja *et al.* "The diagnosis and treatment of chronic rhinosinusitis." *Deutsches Ärzteblatt international,* vol. 121, no. 19, September 2024, pp. 643-651. http://dx.doi.org/10.3238/arztebl.m2024.0167.

[18] Wang, Alice *et al.* "Treatment of granuloma annulare and suppression of proinflammatory cytokine activity with tofacitinib." *Journal of Allergy and Clinical Immunology,* vol. 147, no. 5, May 2021, pp. 1795-1809. http://dx.doi.org/10.1016/j.jaci.2020.10.012.

[19] Liu, Yang Yang *et al.* "Artificial intelligence optimizes the standardized diagnosis and treatment of chronic sinusitis." *Frontiers in Physiology,* vol. 16, March 2025. http://dx.doi.org/10.3389/fphys.2025.1522090.

[20] Wang, Jianwei *et al.* "Individualized airway atomization improves preoperative lung dysfunction in patients with chronic rhinosinusitis with nasal polyps." *International Forum of Allergy & Rhinology,* vol. 12, no. 6, December 2021, pp. 880-882. http://dx.doi.org/10.1002/alr.22924.

[21] Kim, Do Hyun *et al.* "Predictive value of nasal nitric oxide for diagnosing eosinophilic chronic rhinosinusitis: A systematic review and meta-analysis." *American Journal of Rhinology & Allergy,* vol. 38, no. 4, April 2024, pp. 264-271. http://dx.doi.org/10.1177/19458924241251387.

[22] Liang, Yibo *et al.* "Alterations of nasal microbiome in eosinophilic chronic rhinosinusitis." *Journal of Allergy and Clinical Immunology,* vol. 151, no. 5, May 2023, pp. 1286-1295.e2. http://dx.doi.org/10.1016/j.jaci.2022.11.031.

[23] Kim, Hugh Andrew Jinwook *et al.* "Assessing the use of patient-reported outcome measures in the routine clinical care of chronic rhinosinusitis patients: A canadian perspective." *Journal of Otolaryngology - Head & Neck Surgery,* vol. 53, January 2024. http://dx.doi.org/10.1177/19160216241288806.

[24] Jiang, Shirley Y. *et al.* "Medicine resident perceptions regarding β-lactam antibiotic prescribing in patients with penicillin allergy." *The Journal of Allergy and Clinical Immunology: In Practice,* vol. 11, no. 2, February 2023, pp. 638-641.e1. http://dx.doi.org/10.1016/j.jaip.2022. 10.012.

[25] Adel-patient, Karine *et al.* "Immune signatures distinguish frequent from non-frequent exacerbators among children with severe asthma." *Allergy,* vol. 76, no. 7, March 2021, pp. 2261-2264. http://dx.doi.org/10.1111/all.14759.

[26] Cavaliere, Carlo *et al.* "Long-term perspectives on chronic rhinosinusitis with nasal polyps: Evaluating recurrence rates after functional endoscopic sinus surgery in the biologics era—a 5-year follow-up study." *Journal of Personalized Medicine,* vol. 14, no. 3, March 2024, pp. 297-0. http://dx.doi.org/10.3390/jpm14030297.

[27] Martin-Jimenez, Daniel *et al.* "Long-term clinical outcomes in patients with chronic rhinosinusitis with nasal polyps associated with expanded types of endoscopic sinus surgery." *Journal of Clinical Medicine,* vol. 13, no. 3, February 2024, pp. 866-0. http://dx.doi.org/10.3390/jcm13030866.

[28] Algahtani, Saad *et al.* "Outcomes of functional endoscopic sinus surgery in chronic rhinosinusitis: A systematic review and meta-analysis." *Cureus,* vol. 16, no. 2, February 2024. http://dx.doi.org/10.7759/cureus.53952.

[29] Xie, Hui Hui *et al.* "Partial trisomy 16q and partial monosomy 7p of a fetus derivated from paternal balanced translocation." *Medicine,* vol. 100, no. 7, February 2021, pp. e24382-0. http://dx.doi.org/10.1097/md.0000000000024382.

[30] Sharifovna, U.S. "Functional endoscopic sinus surgery (FESS) in chronic rhinosinusitis: advances, techniques, complications, and multidisciplinary management." *EurAsian Journal of Medical and Natural Sciences*. Vol. 4, no. 11, 2024, pp. 63-72. https://doi.org/10.5281/zenodo.14160933

[31] Fassas, Scott N. *et al.* "Sinus surgery and balloon sinuplasty: What do patients want to know?" *Otolaryngology–Head and Neck Surgery,* vol. 167, no. 4, February 2022, pp. 777-784. http://dx.doi.org/10.1177/01945998221076803.

[32] Fadel, Mark A., and Uma S. Ramaswamy. "Evaluation of balloon sinuplasty for the treatment of pediatric chronic rhinosinusitis." *Current Opinion in Otolaryngology & Head & Neck Surgery,* vol. 32, no. 6, October 2024, pp. 424-427. http://dx.doi.org/10.1097/moo.0000000000001016.

[33] Gupta, Ritu. "Balloon sinuplasty: Our experience." *Indian Journal of Otolaryngology and Head & Neck Surgery,* vol. 76, no. 1, July 2023, pp. 141-144. http://dx.doi.org/10.1007/s12070-023-04111-7.

[34] Fernandes, Klecius Leite. "Squamous cell carcinoma of the external auditory canal: A sternocleidomastoid flap reconstruction." *Online Journal of Otolaryngology and Rhinology,* vol. 5, no. 5, October 2022, pp. 1-3. http://dx.doi.org/10.33552/ojor.2022.05.000623.

[35] Zamaili, A.M. *et al.* "The impact of middle meatal steroid-eluting implants on the postoperative outcomes of chronic rhinosinusitis: A systematic review and meta-analysis." *European Annals of Otorhinolaryngology, Head and Neck Diseases,* vol. 142, no. 1, January 2025, pp. 26-37. http://dx.doi.org/10.1016/j.anorl. 2024.02.014.

[36] Shah, Viraj N. *et al.* "Complications associated with propel mometasone furoate bioabsorbable drug-eluting sinus stents from 2012 to 2020." *American Journal of Rhinology & Allergy,* vol. 36, no. 2, August 2021, pp. 185-190. http://dx.doi.org/10.1177/19458924211035641.

[37] Shah, Viraj N. *et al.* "Complications associated with propel mometasone furoate bioabsorbable drug-eluting sinus stents from 2012 to 2020." *American Journal of Rhinology & Allergy,* vol. 36, no. 2, August 2021, pp. 185-190. http://dx.doi.org/10.1177/19458924211035641.

[38] Wu, Dawei *et al.* "Effects of fluticasone exhalation delivery system in patients with chronic rhinosinusitis with nasal polyps: A systematic review." *American Journal of Rhinology & Allergy,* vol. 36, no. 2, August 2021, pp. 176-184. http://dx.doi.org/10.1177/19458924211033214.

[39] Kang, Yun Jin *et al.* "Effectiveness of the exhalation delivery system with fluticasone for treating chronic rhinosinusitis with nasal polyposis: A systematic review and meta-analysis." *European Archives of Oto-Rhino-Laryngology,* vol. 282, no. 4, November 2024, pp. 1709-1718. http://dx.doi.org/10.1007/s00405-024-09073-2.

[40] Leopold, Donald A. *et al.* "Navigate ii: Randomized, double-blind trial of the exhalation delivery system with fluticasone for nasal polyposis." *Journal of Allergy and Clinical Immunology,* vol. 143, no. 1, January 2019, pp. 126-134.e5. http://dx.doi.org/10.1016/j.jaci.2018.06.010.

[41] Ow, Randall A. *et al.* "Efficacy of the exhalation delivery system with fluticasone in patients with chronic rhinosinusitis with nasal polyps whose symptoms recur after sinus surgery." *International Forum of Allergy & Rhinology,* vol. 13, no. 1, June 2022, pp. 31-41. http://dx.doi.org/10.1002/alr.23043.

[42] Wang, Ming *et al.* "New insights into the endotypes of chronic rhinosinusitis in the biologic era." *Journal of Allergy and Clinical Immunology,* vol. 156, no. 1, July 2025, pp. 51-60. http://dx.doi.org/10.1016/j.jaci.2025.02.015.

[43] Striz, Ilja *et al.* "New insights into the pathophysiology and therapeutic targets of asthma and comorbid chronic rhinosinusitis with or without nasal polyposis." *Clinical Science,* vol. 137, no. 9, May 2023, pp. 727-753. http://dx.doi.org/10.1042/cs20190281.

[44] Guo, Cui Lian *et al.* "Type 2 biomarkers for the indication and response to biologics in crswnp." *Current Allergy and Asthma Reports,* vol. 23, no. 12, November 2023, pp. 703-713. http://dx.doi.org/10.1007/s11882-023-01114-w.

[45] Alska, Ewa *et al.* "Advances in biologic therapies for allergic diseases: Current trends, emerging agents, and future perspectives." *Journal of Clinical Medicine,* vol. 14, no. 4, February 2025, pp. 1079-0. http://dx.doi.org/10.3390/jcm14041079.

[46] Ion, Ana *et al.* "Risks of biologic therapy and the importance of multidisciplinary approach for an accurate management of patients with moderate-severe psoriasis and concomitant diseases." *Biology,* vol. 11, no. 6, May 2022, pp. 808-0. http://dx.doi.org/10.3390/biology11060808.

[47] Orlando, Pietro *et al. Sustained efficacy and low rate of adverse events of dupilumab in type-2 Crswnp over 48 months.* 2025. 10.1002/lary.32205, http://dx.doi.org/10.1002/lary.32205. http://dx.doi.org/10.1002/lary.32205.

[48] Heffernan, Austin *et al.* "Non-type 2 and mixed inflammation in chronic rhinosinusitis and lower airway disease." *The Laryngoscope,* vol. 134, no. 3, August 2023, pp. 1005-1013. http://dx.doi.org/10.1002/lary.30992.

[49] Yao, Yin *et al.* "Revisiting asian chronic rhinosinusitis in the era of type 2 biologics." *Clinical & Experimental Allergy,* vol. 52, no. 2, December 2021, pp. 231-243. http://dx.doi.org/10.1111/cea.14065.

[50] Sima, Yutong *et al.* "Precision medicine in chronic rhinosinusitis – using endotype and endotype-driven therapeutic options." *Expert Review of Clinical Immunology,* vol. 19, no. 8, July 2023, pp. 949-958. http://dx.doi.org/10.1080/1744666x.2023.2232115.

[51] Xie, Xiran *et al.* "Diverse endotypes of chronic rhinosinusitis and clinical implications." *Clinical Reviews in Allergy & Immunology,* vol. 65, no. 3, January 2024, pp. 420-432. http://dx.doi.org/10.1007/s12016-023-08976-y.

[52] Yu, Yafang, and Jianwen Yan. "Effectiveness of a multimodal therapy protocol for the management of allergic rhinitis: A randomized controlled trial." *European Journal of Medical Research,* vol. 29, no. 1, December 2024. http://dx.doi.org/10.1186/s40001-024-02210-x.

[53] Taw, Malcolm B. *et al.* "Integrative approach to rhinosinusitis." *Otolaryngologic Clinics of North America,* vol. 55, no. 5, October 2022, pp. 947-963. http://dx.doi.org/10.1016/j.otc.2022.06.004.